Message

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Sent: 5/3/2011 5:28:35 PM
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Subject: NEWS UPDATES: Industry Challenges EPA To Re-Do Non-Cancer Methanol Risk Assessment (Risk Policy Report)

Industry Challenges EPA To Re-Do Non-Cancer Methanol Risk Assessment

Posted: May 2, 2011

Industry is calling on EPA to withdraw and re-do its recently released draft assessment of methanol's non-cancer risks, arguing that the document does not account for natural levels of methanol in the human body, ignores industry-funded studies published just last year, and is based on an inappropriate animal model.

The Methanol Institute wrote EPA research chief Paul Anastas April 28, requesting that he "withdraw the noncancer Integrated Risk Information System (IRIS) assessment of methanol from its current public and peer review cycle. In our view, the current assessment is so fundamentally flawed that to proceed with peer review of the document would be meaningless, and in fact, counterproductive to good scientific process."

EPA released the draft non-cancer Integrated Risk Information System (IRIS) assessment of methanol April 18, following a controversy over data that it relied on in its assessment of the chemical's cancer risks. The agency initially released a draft IRIS document that included assessments of methanol's cancer and non-cancer risks in January 2010. But industry protested the agency's use of data from an Italian lab, the Ramazzini Institute, which EPA used to calculate its cancer potency estimate. Following the National Toxicology Program's review of some of Ramazzini's original methanol slides last spring, EPA announced that was holding four draft IRIS assessments and two published IRIS assessments that reference Ramazzini data until it could further investigate. *Relevant documents are available on InsideEPA.com.*

Last month, the agency announced that it will conduct a Pathology Working Group review of slides of several of the chemicals that Ramazzini studied. The cancer portion of the methanol IRIS assessment is on hold until that more extensive review is complete, but the agency indicated that it would go forward with the non-cancer portion of the methanol assessment. While the cancer portion of the assessment may be more controversial than the non-cancer portion, industry also has concerns with the non-cancer document, and is calling for EPA to re-do the assessment based on newer studies that it funded, noting that the agency has not updated the non-cancer assessment and it is identical to the one it released more than a year ago.

"Your staff has chosen to republish for public comment and peer review these identical pages without any alteration to reflect the changes in the scientific landscape for methanol in the intervening period. These changes require fundamental changes in the analysis of the methanol assessment which promise to radically alter the conclusions of the assessment," the Methanol Institute writes Anastas.

EPA's discussion of how it calculates the reference dose (RfD) also indicates that it considered one of the studies in its cancer risk assessment in its non-cancer assessment, the Soffritti study. The Soffritti study, one of the Ramazzini studies, is not the basis for the RfD calculation, but is referenced in the document. EPA describes it as "the only lifetime oral study available" of methanol, according to the draft assessment. EPA relies on multiple studies, including some where the lab animals inhaled methanol, to calculate the RfD. The agency explains that "given the oral database limitations, including the limited reporting of noncancer findings in the subchronic (U.S. EPA, 1986b) and chronic studies (Soffritti et al., 2002) of rats and the high-dose levels used in the two rodent developmental studies, EPA has derived an RfD by using relevant inhalation data . . ."

"That too is a significant concern," an industry source says. The assessment needs to be revised, include data from industry-funded research at the University of Toronto and go back through intra- and inter-agency review processes, the source says. EPA, instead, has planned a listening session for May 26, and indicated that it will soon announce a date for a peer review of the assessment.

An EPA spokeswoman did not explain why agency staff did not update the assessment before re-releasing it. "EPA is continually identifying new literature related to the health assessment of methanol," the spokeswoman writes *Risk Policy Report* in an email. "The information, analyses and conclusions of the 2011 draft are identical to the non-cancer portions of the draft previously released in January 2010; hence, no new studies were added."

The spokeswoman adds that the industry-funded "studies will be made available to the external peer review panel. Following input by the external peer review panel and the public, EPA will consider these studies as appropriate in the completion of the IRIS methanol assessment for non-cancer health effects."

The draft IRIS document proposes an RfD of 0.4 milligrams per kilogram body-weight per day (mg/kg-day), somewhat stricter than the existing RfD for methanol of 0.5 mg/kg-day, published in 1991. The draft also proposes an reference concentration (RfC) of 2 milligrams per cubic meter. The 1991 assessment did not set an RfC, as the health effects data at that time "were determined to be inadequate for derivation of an RfC," according to the draft document.

Industry argues that these levels are below endogenous levels of methanol -- those that exist naturally in the body -- and that EPA needs to take these levels into account when re-calculating its risk numbers.

In its letter, the Methanol Institute cites the National Academy of Science's recent report on formaldehyde, which raised similar concerns about the endogenous production of that chemical. It quotes the NAS concern that "the endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract."

Such endogenous and food sources of methanol also complicate an assessment of methanol, industry argues. Human background levels appear to range from 0.4 and 4.0 mg/L, a range that overlaps the proposed RfC.

The methanol industry is particularly affronted that the new document does not reference any of the studies stemming from the four-year research program it funded at the University of Toronto into how various species metabolize methanol and how the chemicals causes effects in the body. Several of the papers from the study were published in 2010, and the new draft document indicates that its literature search extended through October 2010. But no changes were made to the principle studies EPA selected as the basis for its quantitative risk estimates, the RfD and RfC, which are unchanged from the 2010 draft that only looked at studies through 2007. The RfD and RfC are the amounts that EPA believes will not cause harm if consumed or inhaled, respectively, over a lifetime.

Methanol industry representatives first met with staff at EPA's National Center for Environmental Assessment, which manages the IRIS

database and develops the assessments in 2005, an industry source says. They discussed data gaps in existing methanol literature problematic to the IRIS assessment, including mode of action, or how methanol causes effects in the body, and how different species of lab animals and humans metabolize methanol. "Based on those conversations, we began a four-year study at the University of Toronto," the source says.

The Canadian research indicates that rodents -- like the lab rats used in the studies that EPA based its risk estimates upon -- are not the best predictors of human health risks from methanol because they metabolize the chemical differently than humans do. "Rabbits are a better predictor of human effects than sensitive strains of mice," the industry source says.

In a report to the Methanol Institute, Peter Wells, a pharmacology professor at the University of Toronto, explains that rodents metabolize methanol by a different process than humans, raising questions about their suitability to predict human risk from the chemical.

"Methanol is teratogenic in rodents, which unlike humans use catalase to convert both methanol to formaldehyde, and its formic acid (FA) metabolite to carbon dioxide and water. It is not known if methanol is developmentally toxic in humans, and it is unclear if rodents can predict human risk in light of their different routes of MeOH metabolism," Wells wrote in his November 2010 report. "These results suggest that the rabbit might be a more accurate model than the mouse for predicting the human risk for MeOH developmental toxicity."

The Methanol Institute adds in its letter that "EPA has no plans to point out these studies to the peer review panel, despite the fact that the proposed reference concentrations are based on rodent studies."

Similarly, the physiologically based pharmacokinetic model that EPA used to extrapolate human RfC and RfD values from the rodent data is also "based on rodent developmental effects in rodents," the industry source says. "Clearly, we think the modeling needs to be re-done." -- *Maria Hegstad*

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